Reaction Between Grignard Reagents and Heterocyclic *N*-oxides

Synthesis of Substituted Pyridines, Piperidines and Piperazines

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Akademisk avhandling

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Title
Reaction Between Grignard Reagents and Heterocyclic *N*-oxides – Synthesis of Substituted Pyridines, Piperidines and Piperazines

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Abstract
This thesis describes the development of new synthetic methodologies for preparation of bioactive interesting compounds, e.g. substituted pyridines, piperidines or piparazines. These compounds are synthesized from commercially available, cheap and easily prepared reagents, videlicet the reaction between Grignard reagents and heterocyclic *N*-oxides.

The first part of this thesis deals with an improvement for synthesis of dienal-oximes and substituted pyridines. This was accomplished by a rapid addition of Grignard reagents to pyridine *N*-oxides at rt. yielding a diverse set of substituted dienal-oximes. During these studies, it was observed that the obtained dienal-oxmies are prone to ring-close upon heating. By taking advantage of this, a practical synthesis of substituted pyridines was developed.

In the second part, an *ortho*-metalation of pyridine *N*-oxides using Grignard reagents is discussed. The method can be used for incorporation of a range of different electrophiles, including aldehydes, ketones and halogens. Furthermore, the importance for incorporation of halogens are exemplified through a Suzuki–Miyaura coupling reaction of 2-iodo pyridine *N*-oxides and different boronic acids. Later it was discovered that if the reaction temperature is kept below -20 °C, the undesired ringopening can be avoided. Thus, the synthesis of 2,3-dihydropyridine *N*-oxide, by reacting Grignard reagents with pyridine *N*-oxides at -40 °C followed by sequential addition of aldehyde or ketone, was accomplished. The reaction provides complete regio- and stereoselectivity yielding *trans*-2,3-dihydropyridine *N*-oxides in good yields. These intermediate products could then be used for synthesis of either substituted piperidines, by reduction, or reacted in a Diels–Alder cycloaddtion to give the *aza*-bicyclo compound.

In the last part of this thesis, the discovered reactivity for pyridine *N*-oxides, is applied on pyrazine *N*-oxides in effort to synthesize substituted piperazines. These substances are obtained by the reaction of Grignard reagents and pyrazine *N*-oxides at -78 °C followed by reduction and protection, using a one-pot procedure. The product, a protected piperazine, that easily can be orthogonally deprotected, allowing synthetic modifications at either nitrogens in a fast and step efficient manner. Finally, an enantioselective procedure using a combination of PhMgCl and (-)-sparteine is discussed, giving opportunity for a stereoselective synthesis of substituted piperazines.

Keywords
Grignard reagents, pyridine *N*-oxide, pyrazine *N*-oxide, dienal-oxime, pyridine, *ortho*-metalation, piperidine, piperazine, asymmetric

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